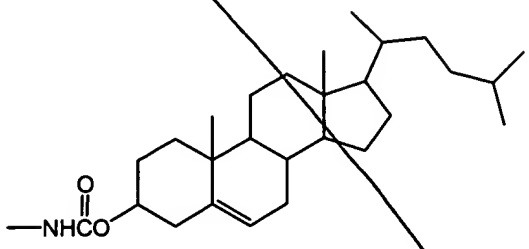
61. The compound according to claim 57, wherein $Y^1$-CHOL and $Y^2$-CHOL have the structure:




62. The compound according to claim 57, wherein $Nu^1$ and $Nu^2$ are nucleotides having an exocyclic amine group to which $-R^5$-D and $-R^6Q$ are attached, respectively.

## REMARKS

**Sequence Information**

On August 1, 2001, Applicant submitted: (a) a computer readable form of the "Sequence Listing" for the nucleic acid sequences set forth in the present application (b) a paper copy of the "Sequence Listing"; and a statement that the content of the paper and computer readable copies are the same; and (c) an amendment identifying the sequences set forth in the application according to their SEQ. ID NO. Thus, Applicant respectfully requests a finding by the Examiner that the requirements under 37 C.F.R. §§1.821-1.825 are satisfied.

**Priority**

Applicant has amended the specification to remove the recitation that the present application is a "continuation in part" of provisional application 60/138,376. Thus, Applicant requests a finding by the Examiner that the priority claim is in order.

**Status of the Claims**

In a Preliminary Amendment filed on September 19, 2000, Applicant amended claims 19 and 26 (*see*, the second full paragraph of page 4 of the Preliminary Amendment). Amended claims 19 and 26 appear to have been substituted for originally filed claims 1 and 2 during examination. It appears that originally filed claims 19 and 26, as well as claims incorrectly thought to be dependent upon these claims were examined on their merits. The replacement of originally

filed claims 1 and 2 with amended claims 19 and 26 resulted in a number of issues arising under 35 U.S.C. § 112, second paragraph.

The replacement of originally filed claims 1 and 2 with amended claims 19 and 26 was not Applicant's intention. The Preliminary Amendment does not explicitly request that originally filed claims 1 and 2 be replaced with amended claims 19 and 26, nor were originally filed claims 1 and 2 canceled. Moreover, the marked up versions of claims 19 and 26 (labeled 1 and 2, respectively) do not correspond to the text of the originally filed claims 1 and 2.

To clarify the status of the claims, Applicant has canceled the pending claims and substituted them with the claim set above. Thus, claims 1-31 are canceled. New claims 32-62 are submitted herewith. Each of new claims 32-62 is a substantial duplicate, some with minor amendments, of a claim originally filed or, in the case of claims 50 and 57, amended by the Preliminary Amendment submitted on September 19, 2000. A one-to-one correspondence exists between the numbering of the newly submitted claims and the originally filed claims (e.g., new claim 32 corresponds to originally filed claim 1).

Other than those brought about by the change in claim numbering and dependence, the changes introduced by the new claims are slight. The dependence of claim 62 is changed such that it is now dependent upon the independent claim 57. Claim 58 is amended relative to its originally filed counterpart, claim 27, by removing the term "substituted or unsubstituted alkyl" from the Markush group, thereby further limiting claim 58 relative to claim 57. In claim 50, the term "heteroalkyl" appears in the Markush grouping for $R^1$, $R^2$, $R^3$ and $R^4$. In originally filed claim 19, this term was incorrectly spelled as "heteroalky."

Claims 50 and 57 recite that "each CHOL interacts with the other CHOL to bring D and Q into operative proximity, thereby enabling transfer of energy from D to Q." This feature was not recited in the corresponding originally filed claims 19 and 26. Support for the amendment is found in the specification at, for example, page 5, lines 18-20.

New claim 45 has been changed relative to the corresponding originally filed claim 14 by the addition of an explicit recitation of the elements of hybridizing the nucleic acid and the probe of the invention and amplifying the nucleic acid. Support for this amendment is found at page 41, lines 26-33 through page 42, lines 1-5. No new matter is added by the amendment.

New claim 47 has been changed relative to the corresponding originally filed claim 16 by the addition of an explicit recitation of the elements of hybridizing the nucleic acid and the

probe of the invention and detecting a change in fluorescence of the probe. Support for this amendment is found at page 42, lines 29-35. No new matter is added by the amendment.

**The Invention**

Applicant has invented a nucleic acid probe having a molecular energy donor and molecular energy acceptor pair bound to the nucleic acid. The probe also includes a pair of stabilizing moieties that are attached to the nucleic acid probe. The stabilizing moieties function to bring the energy donor and the energy acceptor into operative proximity, thereby enabling transfer of energy from the donor to the acceptor.

When the nucleic acid sequence of the probe is not hybridized to a complementary nucleic acid strand, the probe emits minimal amounts of signal (e.g., fluorescence), because the energy donor is quenched by the energy acceptor. The stabilizing moieties function to bring the energy donor and the energy acceptor into sufficient proximity that the quenching interaction can occur. When the nucleic acid portion of the probe is hybridized to a complementary nucleic acid strand, the interaction of the stabilizing moieties is disrupted, moving the energy donor and the energy acceptor to a distance away from each other that is sufficient to allow detection of signal emitted by the energy donor.

**Objection Under 37 CFR §1.73(c)**

Claim 27 was objected to under 37 CFR §1.73(c), as being of improper dependent form. Claim 27 is canceled, rendering the objection moot. Therefore, Applicant requests the withdrawal of this objection. Moreover, newly introduced claim 58 (corresponding to originally filed claim 27) is amended to remove the term "substituted or unsubstituted alkyl," thereby further limiting claim 58 relative to claim 57 from which it depends. Thus, a similar objection to claim 58 would be improper.

**The Rejections**

**Under 35 U.S.C. § 112, second paragraph**

Claims 3-8, 12, 14-17, 20 and 31 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-15 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting an essential step, the omission of which does not set forth the method in clear and unambiguous terms. New claim 45 explicitly recites the missing steps. Thus, Applicant requests withdrawal of the

Claims 16-17 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms.

Each of the claims rejected under 35 U.S.C. § 112, second paragraph is canceled rendering moot the rejections above. Thus, Applicant requests the withdrawal of these rejections.

Regarding the rejections of claims 14-17, newly submitted claims 45-48 correspond to originally filed claims 14-17. The newly submitted claims explicitly recite the missing elements. Therefore, Applicant submits that a rejection of claims 45-48 under 35 U.S.C. § 112, second paragraph as being incomplete for omitting an essential step would be improper.

**Under 35 U.S.C. § 103(a)**

***Over Meade et al. in view of Manhorran et al. and Gold et al.***

Claims 1-3, 6-11, 13-26 and 28-30 are rejected under 35 USC §103(a) as being unpatentable over Meade, *et al.*("Meade"), in view of Manoharan, *et al.* ("Manhorran") and Gold, *et al.* ("Gold"). Although each of the rejected claims is canceled rendering the rejection moot, Applicant asserts that a similar rejection of the claims now pending would be improper for the reasons set forth below.

The Examiner characterizes Meade as disclosing nucleic acid molecules comprising electron donor and electron acceptor moieties covalently bound to the ribose phosphate backbone of the nucleic acid. The electron donors include both transition metal chelates and organic electron donors. Meade also is characterized as setting forth a method of using the disclosed probes in nucleic acid amplification. The Examiner admits that Meade does not disclose or suggest the use of an electron donor and an electron acceptor in conjunction with a cholesterol derivative or a cholesterol –NHC(O)-O-PEG group.

Manhorran is characterized as disclosing sequence specific oligonucleotides that include functionalized nucleotides having substituents such as steroids, reporter molecules. When the substituents are steroids, Manhorran discloses that the steroid is selected from cholic acid, deoxycholic acid, dehydrocholic acid, cortisone, testosterone, cholesterol and digoigenin. The

modified nucleic acids of Manhorran are disclosed as having improved ability to cross cell membranes relative to their unmodified analogs. The Examiner states that Manhorran does not expressly teach linking of cholesterol moieties to nucleic acids using a PEG linker.

The Examiner characterizes Gold as disclosing methods of preparing derivatized nucleic acids for diagnostic and therapeutic applications. The Examiner focuses on Gold's disclosure of a nucleic acid derivatized with both a photoactive group, e.g., fluorescein and a lipophilic group, such as cholesterol.

The Examiner has concluded that it would have been *prima facie* obvious to modify the probes of Meade with the cholesterol groups taught by either Manhorran or Gold. It is further asserted that one of skill would have found the invention as claimed to be obvious because the prior art discloses electron donor and acceptor modified oligonucleotides and methods for introducing cholesterol modifications at the non-terminal nucleotides of a nucleic acid chain. The Examiner further concludes that one of ordinary skill would have been motivated to modify the nucleic acid probes of Meade with the lipophilic groups of Manhorran and Gold, because the modified oligonucleotides of Manhorran and Gold are disclosed as useful for the same purpose, particularly for diagnostic purposes, and the modifications of Manhorran and Gold would confer enhanced pharmaceutical properties to the nucleic acid probes of Meade.

For the reasons set forth below, Applicant respectfully asserts that the Examiner has not set forth a proper *prima facie* case of obviousness for any of the claims now pending.

**A. The Invention Must be Considered as a Whole**

As the Examiner is aware, the invention as a whole must be considered in determining the non-obviousness of an invention (MPEP §2141.02). The Examiner has provided and analyzed three references. The references variously disclose nucleic acids derivatized with lipophilic groups, fluorescent agents and an energy transfer pair. Applicant does not merely claim a nucleic acid having an energy transfer pair and a lipophilic group. In the claims presented herein, the Applicant sets forth a compound in which the non-nucleic acid stabilizing moieties (e.g., cholesterol) interact with each other to bring the energy donor and the energy acceptor into operative proximity, thereby enabling transfer of energy from the donor to the acceptor. The Applicant respectfully asserts that this feature is neither disclosed nor suggested in any of the cited references.

**B. A Proper *Prima Facie* Case of Obviousness Cannot b Set Forth Based Upon the Ref r nces of Record**

To construct a *prima facie* case of obviousness, the Examiner must meet three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations. *See*, MPEP §2142. Moreover, to avoid the pitfall of hindsight, the Examiner must "identify ***specifically***...the reasons one of ordinary skill in the art would have been motivated to select the references and combine them," *In re Rouffet* 47 USPQ2d 1453, 1459 (Fed. Cir. 1998). Applicant respectfully submits that each of the required criteria set forth above have not been satisfied, thus, a *prima facie* case of obviousness has not been set forth.

***1. There is no Motivation to Combine the Cited References***

The Applicant recognized that including non-nucleic acid stabilizing groups (e.g., cholesterol) and an energy donor and acceptor pair in the structure of a nucleic acid would result in the nucleic acid adopting a conformation in which the energy donor is sufficiently proximate the energy acceptor to transfer energy to the acceptor. None of the cited references disclose or suggest using stabilizing moieties to alter the conformation of a nucleic acid and bring the members of an energy transfer pair into operative proximity. Moreover, none of the cited references suggest that any advantage would accrue from attaching groups onto a nucleic acid that alter its conformation.

Meade teaches a nucleic acid derivatized with an electron transfer donor and acceptor. Meade neither discloses nor suggests altering the conformation of the nucleic acid by the use of stabilizing groups to bring the donor and acceptor into proximity. Furthermore, Meade does not suggest that the energy transfer pair would function more efficiently if the nucleic acid conformation were altered. Meade does not disclose that there is any deficiency in the disclosed invention that might be remedied by combining it with elements of the secondary references, nor does Meade suggest that any advantage would result from the combination.

Regarding the secondary references, Manhorran discloses nucleic acids derivatized with one or more lipophilic groups. Manhorran does not disclose or suggest a nucleic acid derivatized with lipophilic groups and an energy transfer pair. Gold discloses nucleic acids derivatized through a PEG linker with a lipophilic group. Neither, Manhorran nor Gold recognize

that the presence of two lipophilic groups on a nucleic acid can be used to alter the nucleic acid conformation in a manner that brings an attached energy transfer pair into operative proximity. Moreover, neither Manhorran nor Gold suggest that the disclosed inventions are deficient in any manner that could be ameliorated by combining the lipophilic nucleic acids with an energy transfer pair.

In view of the lack of motivation to combine the references, Applicant submits that the Examiner has located certain elements of Applicant's claimed invention in the art and combined them because it is theoretically possible to do so. Such a combination is the hallmark of hindsight. As the Examiner is aware, a motivation to modify a reference ***must be based on what is desirable, not just on what is feasible***. *Winner International Royalty Corp. v. Wang*, 98-1553, page 17 (Fed. Cir., Jan. 27, 2000). None of the cited references suggest that it would be desirable to combine two lipophilic groups and an energy transfer pair on a nucleic acid backbone to bring the members of the energy transfer pair into operative proximity. As there is no motivation to combine the references, a rejection of the pending claims over the combination of the cited references would be improper.

### 2. *The Combination of References is Missing Elements of Applicant's Claims*

Applicant has demonstrated that the references fail to motivate their combination. Moreover, even if the combination of references was proper, the combination would not suggest Applicant's invention, because the combination does not disclose every element of Applicant's claimed invention.

Each of the claims now pending is dependent from a claim that recites that the non-nucleic acid stabilizing groups interact to bring the components of the energy transfer pair into operative proximity so that the donor can transfer energy to the acceptor. This element is not disclosed or suggested in any of the cited references. Thus, a proper *prima facie* case of obviousness cannot be set forth for the pending claims based on the cited references.

### 3. *There is no Reasonable Expectation of Success*

As set forth above, the art did not recognize that non-nucleic acid stabilizing groups (e.g., cholesterol) could be used to bring an energy donor and an energy acceptor conjugated to a nucleic acid into operable proximity, thereby allowing energy transfer to occur. As there was no

recognition of this feature of Applicant's invention in the art as exemplified by the cited references, there could have been no reasonable expectation of success associated with Applicant's endeavor. Applicant respectfully submits that the only expectation of success associated with the present invention is that found within Applicant's own specification.

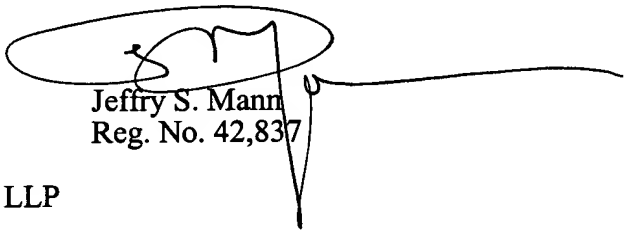
In view of the remarks set forth above, Applicant respectfully asserts that the present claims are patentably non-obvious over the improper combination of the cited references. Therefore, Applicant submits that a similar rejection of the claims now pending over the cited references would be improper.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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SF 1227077 v1

## MARKED-UP SPECIFICATION

On page one, line 5, delete the first paragraph below:

[This application is a Continuation-in-Part of U.S. Provisional application Serial No. 60/138,376, filed on June 9, 1999, the disclosure of which is incorporated herein in its entirety for all purposes.].

On page one, line 5, insert the following:

--This application claims the benefit of U.S. Provisional Application No. 60/138,376, filed on June 9, 1999, the disclosure of which is incorporated herein in its entirety for all purposes.--